REMARKS

By this Amendment, Applicant has previously canceled claims 1-66 without prejudice to the Applicant's right to pursue these matters in a future application. Applicant has added new claims 88-119. Support for new claims 88-119 can be found *inter alia* in the cancelled claims 1-66 and previously presented claims 67-87.

Further, support for "synergistic therapeutic effect" and "synergistically effective amount of orally-administered glucan" in claims 67, 89 and/or 107 can be found *inter alia* on page 41, lines 33-34 of the specification.

Further, support for the term "foreign to the immune system of a host or mammal" in claims 67, 89 and/or 107 can be found *inter alia* on pages 81-82 of the specification.

Accordingly, there is no issue of new matters, and Applicant respectfully requests the entry of this Amendment. Upon entry, claims 67-119 are pending under examination.

1. Objection to the Specification

The Examiner objected to the Specification. The Examiner states:

> There is no brief description of the drawings section pursuant to the provisions of 37 CFR 1.74. Explanation of the drawings must be in this section and not scattered throughout the general disclosure.

In response, Applicant respectfully maintains that the explanations of the drawings are located in the "Detailed Description of the Figures" section of the Specification. *See*

pages 7-15 of the Specification. 37 CFR 1.74 states "when there are drawings, there shall be a brief description of the several views of the drawings." Applicant respectfully directs the Examiner's attention to the "Detailed Description of the Figures" section on pages 7-15 of the Specification, which contains the explanations of the figures. Also, for clarity, the figures are grouped under the subheadings of the corresponding experiments to which they pertain, i.e., "First Series of Experiments, Second Series of Experiments, etc..." Therefore, Applicant respectfully requests the reconsideration and withdrawal of this ground of objection.

2. Rejection Under 35 U.S.C. Section 102(B)

The Examiner rejected claims 67, 80, 82-85 under 35 U.S.C. section 102 as being anticipated by U.S. Pat. No. 5,849,720 issued to Jamas, et al.

The Examiner states:

> James et al. [sic] teach a composition comprising an effective amount of orally administered glucan that is capable of enhancing efficacy of antibodies (*see* column 4, lines 54-64). *See* page 3, section B of the December 17, 2004 Office Action.

Column 4, lines 54-64 of Jamas et al. states:

> PGG is a non-toxic, non-antigenic glucan preparation which enhances or primes the body's natural defense against infection, particularly for patients with normal or decreased immunologic function, so that the normal immune response is faster and more pronounced. Parenteral administration of PGG mimics the natural physiological response to an infectious challenge by enhancing the balanced, endogenous release of cytokines

> in appropriate quantities and proportions. PGG can be used for the prevention and treatment of infections caused by a broad spectrum of bacterial, fungal, viral and protozoan pathogens.

2.1 One of ordinary skill in the art would not use PGG-glucan to practice Applicant's claimed invention

In response, Applicant respectfully traverses the Examiner's above ground of rejection. Applicant maintains that PGG was shown in a clinical trial to have marginal effect in reducing the incidence of serious infections among patients who underwent gastrointestinal surgery, although the exact mechanism of PGG action in these patients was unknown. *See* page 977, first sentence under paragraph heading "Results" of Dellinger et al. Effect of PGG-glucan on the Rate of Serious Postoperative Infection or Death Observed after High-Risk Gastrointestinal Operations. Arch Surg. Vol. 134, p. 977-983 (1999). A copy of Dellinger et al. is attached herein as **Exhibit A**.

Column 4, lines 54-64 of Jamas et al., as cited by the Examiner, states:

> *PGG is a **non-toxic, non-antigenic** glucan preparation {emphasis}* which enhances or primes the body's natural defenses against infection...

However, contrary to the assertion by Jamas et al., a clinical study using PGG-glucan was terminated because PGG-glucan exhibited marginal clinical benefit and caused adverse side effects. *See* Abstract of Dellinger et al. The toxicity of PGG is expected to increase if PGG dosage is increased. *See* page 977, last sentence under paragraph heading "Results" of Dellinger et al., **Exhibit A**.

PGG-glucan was shown to be toxic in a large clinical trial in gastrointestinal post-operative patients. "Study drug was stopped owing to adverse effects more frequently for patients receiving PGG-glucan than placebo (2%, 4%, and 7% for the placebo group, 0.5-mg/kg PGG-glucan group, and 1.0-mg/kg PGG-glucan group, respectively, P<.003)." *See* page 977, last sentence under paragraph heading "Results" of Dellinger et al., **Exhibit A**. "All randomized patients revealed no difference in serious infections and deaths in the treated groups compared with placebo groups (15% vs 14%, P>.90)." Only benefit was shown for the noncolorectal malnourished subgroup. *See* page 77, first sentence under paragraph heading "Results" of Dellinger et al., **Exhibit A**.

Results of this study with 1,249 patients, which were published in 1999 and which demonstrated that PGG-glucan produced adverse effects, were contrary to the results obtained in the Phase I and/or II trials using PGG-glucan. For the published results of the Phase I and/or II trials using PGG-glucan, see Babineau et al. A Phase II Multicenter, Double-blind, Randomized, Placebo-Controlled Study of Three Dosages of an Immunomodulator (PGG-Glucan) in High-Risk Surgical Patients. Arch Surg. Vol. 129, p. 1204-1210 (1994), attached herein as **Exhibit B**. *See also* Babineau et al. Randomized Phase I/II Trial of a Macrophage-Specific Immunomodulator (PGG-Glucan) in High-Risk Surgical Patients. Annals of Surgery. Vol. 220, No. 5, p. 601-609 (1994), attached herein as **Exhibit C**.

Based on the negative results obtained from the latest clinical trial (1999) using PGG-glucan, no person of ordinary skill in the art would attempt to administer PGG-glucan to any subject. This may explain why no attempt was made by other investigators to use PGG parenterally again.

The Examiner further states:

> Jamas et al. teach the use of said composition paired with a pharmaceutically acceptable carrier (*See* column 5, example 1) Jamas et al. teach glucan derived from yeast, bacteria, fungi and plants (column 1, lines 13-15). *See* page 3, section B of the December 17, 2004 Office Action.

Column 1, lines 13-15 of Jamas et al., as cited by the Examiner, states:

> Glucans are generally described as polymers of glucose and are derived from yeast, bacteria, fungi, and plants. Glucans containing a β(1-3)-linked glucopyranose backbone…

In response, Applicant respectfully traverses the Examiner's above ground of rejection. Applicant maintains that glucan containing only the β(1-3) backbone will not enhance the efficacy of any antibodies.

The Examiner further states:

> Jamas et al. teach the glucan to be of high molecular weight ranging from 10,000 to 500,000 daltons (column 4, lines 23-25), which is stable to heat treatment (*see* examples 1 and 2, column 5 and 6). *See* page 3, section B, lines 5-7 of the December 17, 2004 Office Action.

In response, Applicant respectfully traverses the Examiner's above ground of rejection. To be effective, and as stated, for example, in Applicant's specification on page 26, lines 23-24, and on page 5, lines 26-29, the glucans need to be at least 100,000 Daltons and preferably 250,000-450,000 Daltons. *See also,*

For example, page 9, lines 10-27 of the Specification and Figures 9-10.

In addition, Applicant has amended claim 67 to add antibodies "which are foreign to the immune system of a host". Therefore, claim 67 and the new claims do not contain the above mentioned issues raised by the Examiner, thereby rendering this ground of rejection moot.

Furthermore, Applicant respectfully maintains that column 4, lines 54-64, of Jamas et al. as cited by the Examiner does not disclose or anticipate Applicant's claimed invention for the reasons given below:

2.2 Applicant's Claimed Invention

Independent claim 67, 89 and 107 recite:

> 67. A composition comprising a synergistically effective amount of orally-administered glucan comprising 1,3-β-backbone with mixed linkages capable of enhancing efficacy of antibodies, which are foreign to the immune system of a host.
>
> 89. A composition for achieving a synergistic therapeutic effect in a mammal in need thereof comprising:
>
> (a) a glucan comprising 1,3-β-backbone with mixed linkages; and
>
> (b) a antibody which is foreign to the immune system of the mammal, and which is effective against cancer or tumor cells,
>
> wherein the synergistic therapeutic effect is the eradication or suppression of cancer or tumor cells; wherein the glucan is orally administered to said

mammal; wherein the glucan is administered concurrently or sequentially with the antibody to said mammal; and wherein the efficacy of the antibodies to eradicate or suppress cancer or tumor cells is synergistically enhanced by the orally administered glucan.

107. A composition for achieving a synergistic therapeutic effect in a mammal in need thereof comprising:

(a) a glucan comprising 1,3-β-backbone with either 1,3-1,4 or 1,3-1,6 mixed linkages; and

(b) a antibody which is foreign to the immune system of the mammal, and which is effective against cancer or tumor cells,

wherein the synergistic therapeutic effect is the eradication or suppression of cancer or tumor cells; wherein the glucan is orally administered to said mammal; wherein the glucan is administered concurrently or sequentially with the antibody to said mammal; wherein the efficacy of the antibodies to eradicate or suppress cancer or tumor cells is synergistically enhanced by the orally administering glucan; wherein the glucan has high viscosity and high molecular weight; and wherein the molecular weight of the glucan is at least 100,000 Daltons.

Other claims are depending on the above three independent claims.

Applicant respectfully maintains that Jamas et al. does not disclose or teach "[a] composition comprising a synergistically effective amount of orally-administered glucan comprising 1,3-β-backbone with mixed linkages capable of enhancing efficacy of antibodies, which are foreign to the immune system of a host." Rather, Column 4, lines 54-64 of Jamas et al. as cited by the Examiner simply describe or disclose a glucan preparation which "enhances or primes the *body's natural defense* {emphasis} against infection." Jamas et al. does not teach synergistically

enhancing foreign antibodies, which are introduced into the immune system of a host or subject to treat certain cancers and other life-threatening conditions, concurrently or sequentially with orally-administered glucan.

Furthermore, column 4, lines 54-64 of Jamas et al. as cited by the Examiner only states that "parenteral administration of PGG mimics the natural physiological response to an infectious challenge by enhancing the balanced, endogenous release of cytokines in appropriate quantities and proportions," and does not provide any teaching to one of ordinary skill in the art to combine orally-administered glucan with foreign antibodies to synergistically enhance the efficacy of the foreign antibodies in a host or subject.

2.3 Jamas et al. teach one of ordinary skill away from Applicant's claimed invention

Applicant's claimed invention does not produce induction of cytokine release, and therefore, the oral glucan of Applicant's claimed invention can be dose escalated without side effects. This is not obvious from the disclosure of James et al. Orally administered glucan does not stimulate increases in circulating cytokines (IL-12 and TNF). *See* page 1219, last sentence under paragraph heading "Results" of Cheung NK, Modak S. Oral (1,3),(1,4)-β-D-glucan synergizes with Antiganglioside GD2 monoclonal antibody 3F8 in the Therapy of Neuroblastoma. Clinical Cancer Research. Vol. 8, p. 1217-1223 (2002), stating that "[t]here was no detectable serum IL-12 or TNF-α release after p.o. β-glucan administration." A copy of Cheung et al. is attached herein as **Exhibit D**.

2.4 Oral route is not an obvious extension of parenteral route

Moreover, a reference that discloses or teaches administration of biologics by parenteral route does not provide enabling disclosure or teaching to one of ordinary skill in the art to administer such biologics by oral route, or vise versa, because of the vast differences in pharmacodynamics. For example, cytokines, antibodies, and LPS, although possessing potent biologic effects when administered parenterally or subcutaneously have little or no effect when administered orally. Most proteins have to be encapsulated, e.g., in hydrogels in order for them to be bioavailable.

In this case, Jamas et al. does not disclose or teach that glucans will suffice on their own to be bioavailable when given orally. For the immune system, instead of inducing immune activation, orally administered antigens induce profound immune tolerance, an art that is exploited for treating allergies and autoimmune diseases. *See* page 407, second column, first sentence of Mayer L, Shao L. Therapeutic potential of oral tolerance. Nat Rev Immunol. Vol. 4, p. 407-19 (2004), stating that "because oral administration of antigen can lead to systemic unresponsiveness, it is a potentially powerful tool for the therapy of autoimmunity… conditions." A copy of the Mayer et al. is attached herein as **Exhibit E**.

Accordingly, oral administration of biologics is not an obvious application of intravenous injections because of the complex underlying immune mechanisms involved. Another example is intravenous chemotherapy. Although highly effective in cancer treatment, few are as effective when administered orally, and side effects can be equally devastating. Thus, ORAL ROUTE IS NOT

AN OBVIOUS EXTENSION OF THE PARENTERAL ROUTE FOR THERAPEUTICS IN IMMUNOLOGY AND CANCER THERAPY *{emphasis}*.

Therefore, Applicant respectfully requests the reconsideration and withdrawal of this ground of rejection.

3. Rejection Under 35 U.S.C. Section 103(A)

3.1 Applicable Legal Standards for Determining Obviousness Under 35 U.S.C. Section 103

To reject claims in an application under U.S.C. § 103, an un-rebutted prima facie case of obviousness must be established by an examiner. In Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 U.S.P.Q (BNA) 459, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966), the Supreme Court articulated the four (4) factual inquiries for determining obviousness under 35 U.S.C. § 103(a), namely:

(1) the scope and content of the prior art;
(2) the differences between the prior art and the claimed invention;
(3) the level of ordinary skill in the field of the invention; and
(4) an objective indicia such as (i) commercial success, (ii) long felt need, (iii) unexpected results created by the claimed invention, (iv) copying by others, (v) licensing to others, (vi) skepticism of skilled artisans or (vii) failure of others. *In re Rouffet*, 149, F.3d 1350, 1355 (Fed. Cir. 1998).

Most if not all inventions arise from a combination of old elements. *See In re Rouffet* at 1357. Thus, most elements of a claimed invention may often be found in the prior art. *See* id. 1357. When the claimed invention is made by combining known components to achieve a new system, the prior art must provide a ***suggestion or motivation*** to make such a combination *[emphasis added]*. *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1351 (Fed. Cir. 1998)(quoting Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072 (Fed. Cir. 1993)). It is insufficient that prior art shows similar components, unless it also contains some teaching, suggestion, or incentive for arriving at the claimed structure. *Id.* at 1351 (quoting Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 934 (Fed. Cir. 1990)). It is impermissible to reconstruct the claimed invention from selected pieces of prior art absent some suggestion, teaching, or motivation in the prior art to do so. *C.R. Bard, Inc. v. M3 Systems, Inc.* at 1352. The examiner may not use the claimed invention as a blueprint to elements in the prior art to defeat the patentability of the claimed invention. *In re Rouffet* at 1357.

To prevent the use of hindsight based on the invention to defeat patentability of the invention, the examiner must show reasons that a person of ordinary skill in the art, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior references for combination in the manner claimed. *Id.* at 1357.

Motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art, or, in some cases the nature of the

problem to be solved. *In re Werner Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). Teaching, motivation or suggestion may also be implicit from the prior art as a whole. *Id.* at 1370. The test for an implicit showing is what the combine teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art. *Id.* at 1370.

3.2 Claims 68-79 and 83 are <u>not obvious</u> over Jamas et al., Herlyn, Yan et al., Marciani, Cheever et al., Chu et al., and Lane et al.

In the instant Application, the Examiner rejected claims 68-79 and 83 under 35 U.S.C. section 103(a) as being unpatentable over U.S. Pat. No. 5,849,720 issued to Jamas et al., U.S. Pat. No. 5,130,127 issued to Dorothee Herlyn, Yan et al., U.S. Pat. No. 6,573,245 issued to Marcinai, U.S. Pat. No. 6,664,370 issued to Cheever et al., Chu et al., and Lane et al.

The Examiner states:

> James et al. [sic] teach the limitations of claim 67. Jamas et al. does not teach the limitations found in claim 68-72, and 79. Dorothee Herlyn teaches a monoclonal tumor-binding antibody against cancer, which is capable of activating complement. Dorothee Herlyn teaches an antibody capable of activating the antibody dependent cell-mediated cytotoxicity. Additionally, Herlyn teaches the cancer to be melanoma or colon cancer.
>
> *See* page 5, paragraph B, of the December 17, 2004 Office Action.

In response, Applicant respectfully traverses Examiner's above ground of rejection. Jamas et al. may have disclosed "a method for producing high molecular weight, soluble glucan polymers," and Herlyn may have disclosed "a monoclonal tumor-binding antibody against cancer, which is capable activating complement." *See* page 5, paragraph B, of the December 17, 2004 Office Action. However, neither Jamas et al. nor Herlyn, alone or in combination, teach a composition comprising both glucan and antibodies, wherein the glucan is capable of synergistically enhancing the efficacy of antibodies and the glucan is administered to a subject orally.

For the reasons stated in Section 2.1 above and further elaborated below, Applicant respectfully maintains that, by considering the teachings of Jamas et al. and Herlyn, alone or in combination, one of ordinary skill in the art would not have reason to expect success in combining oral glucan of Applicant's claimed invention with intravenously administered monoclonal antibody because:

1. No successes have been demonstrated or reported in animals or in humans of combinations of PGG or lentinan plus monoclonal antibodies despite the wide availability of FDA approved antibodies and the availability of PGG and lentinan for intravenous use.

2. Intravenously administered PGG and intravenously administered lentinan can be toxic because of massive cytokine release.

3. Orally administered lentinan (>1,000,000 Daltons) is too big to have the desirable affinity for CR3 and the

desirable clinical toxicity spectrum when combined with monoclonal antibodies. Large molecular weight glucans (soluble or particulate) administered intravenously often cross-link CR3 and stimulate neutrophil degranulation as well as cytokine release from macrophages. With such toxicity, the intravenous dosage was reduced, thereby compromising its therapeutic potential. On the other hand, small molecular weight glucans were rapidly excreted by renal clearance.

See Summary on page 81 of Sortwell et al. Chronic intravenous administration of lentinan to the rhesus monkey. Toxicol Lett. Vol. 1, p. 81-5 (1981), stating that "[t]he prolonged effects of overdosage with lentinan in the rhesus monkey are associated with foam cell reactions in lung, liver, kidney, spleen, lymph nodes and bone marrow and with varying degrees of vasculitis and associated reactions. A dose level of 0.5 mg/kg/day was without adverse effect." A copy of Sortwell et al. is attached herein as **Exhibit F**.

See also abstract of Shimazu et al. "Intravenous chronic toxicity of lentinan in rats: 6-month treatment and 3-month recovery." J Toxicol Sci. 1980 Dec;5 Suppl:33-57, stating that "[c]hronic toxicity of lentinan was studied in male and female JCL : SD rats. Lentinan was given intravenously into tail vein. Dosage levels employed were 0 (5% mannitol), 0.01, 0.1, 1 (with or without dextran), and 10 mg/kg/day for 6 months in a volume of 1 ml/100 g body weight. After 6 months, the treatment was discontinued and a recovery study was performed for 3 months. Rats receiving 10 mg/kg had redness and necrosis of the tail,

the treatment was stopped at week 5, and the rats were sacrificed. Rats receiving 1 mg/kg showed redness of the ear, tail, and scrotum, which was remarkable in the 2nd and 3rd months. Body weight gains were not adversely affected. Laboratory examinations revealed an increase in leukocyte count, decreases in differential eosinophil count and platelet count, and an increase in serum beta-globulin level in drug-treated rats. At autopsy after 6 months, rats from the drug-treated groups had pulmonary hemorrhage and enlargements of the spleen and mesenteric lymph nodes. Histologic changes attributable to treatment included (1) activation of reticulo-endothelial system such as small epithelioid cell nodule in the liver, spleen, and mesenteric lymph nodes, and mobilization of Kupffer cells; (2) arteritis in various organs, especially notable in the spleen, testis, and epididymis; (3) hemorrhage in the lung; and (4) hypospermatogenesis. All these changes described above had a propensity to recover. The maximum no effect level was estimated to be less than 0.01 mg/kg in the present study in male and female rats." A copy of Shimazu et al. is attached herein as **Exhibit G**.

4. Both PGG and lentinan rely on an intact immune system. Oral glucan of Applicant's invention does not. For proof of principle, only deficient mice were used (both B-cell deficient and T-cell deficient). *See* page 562, last paragraph, lines 16-32 of Cheung et al., Orally administered β-glucans enhance anti-tumor effects of monoclonal antibodies. Cancer Immunol Immunother. Vol. 51, p. 557-564 (2002), stating that "β-glucans function in tumor therapy by binding to CR3 in vitro to mediate leukocyte CR3-dependent cytotoxicity, and that neither T

nor B cells are needed". A copy of Cheung et al. is attached herein as **Exhibit H**.

5. Oral lentinan activates T cells, but also causes T cells to tolerate lentinan after 8 weeks of administration. *See* Summary on page 1567, last sentence, and Figures 1-4 of Hanaue et al. Basic studies on Oral Administration of Lentinan (I)--Influence On Lymphocyte Subsets in peripheral venous blood Nippon Gan Chiryo Gakkai Shi. Vol. 24, p. 1566-1571 (1989), stating that "[o]ral administration of [lentinan] apparently modulates the systemic immune function through T cell stimulation, especially Th cells, but continued administration may induce tolerance to the effect of lentinan." A copy of Hanaue et al. is attached herein as **Exhibit I**. *See also* fourth page, second column, lines 17-21 of Hanaue et al. Effects of Oral Lentinan on T-cell Subsets in Peripheral Venous Blood. Sep-Oct;11(5) (1989),stating that "[t]he absence of an immunomodulatory effect after eight weeks of oral lentinan may be due to a tolerance in rats with normal immune function." A copy of Hanaue is attached herein as **Exhibit J**.

6. Oral lentinan also has little activity. *See* abstract on page 4 and page 6, lines 6-8 of Kidd PM. The use of mushroom glucans and proteoglycans in cancer treatment. Altern Med Rev. Vol. 5, p. 4-27 (2000), stating that lentinan has "little oral activity" and that oral bioavailability of lentinan is limited; "thus it has been routinely administered intravenously." A copy of Kidd is attached herein as **Exhibit K**.

7. Lentinan induced anti-tumor effect is T-cell and cytokine dependent. *See* page 466, second sentence under paragraph heading "Immunological Activities of Lentinan" of Suzuki et al. Antitumor and immunological activity of lentinan in comparison with LPS. Vol. 16, p. 463-468 (1994), stating that "[l]entinan augments the generation of antigen-specific cytotoxic T-lymphocytes (CTLs)... through augmentation of CTLs' responsiveness to IL-2 [cytokine]." A copy of Suzuki et al. is attached herein as **Exhibit L.** *See also* page 437, second sentence under paragraph heading "Cytotoxic T Lymphocytes and Lentinan" of Chihara et al. Antitumor and Metastasis-Inhibitory Activities of Lentinan as an Immunomodulator: An Overview. Cancer Detect Prev Suppl. Vol. 1, p. 423-443 (1987), stating that "[t]he augmented cytokine production, induced by lentinan, apparently stimulates generation of effector cells against tumor cells. This mode of action suggests the requirement of an intact T cell compartment for the antitumor activity of lentinan." A copy of Chihara et al. is attached herein as **Exhibit M.**

In addition, Applicant has found that lentinan glucan, as taught by Herlyn, when administered orally did not synergize well or enhance the efficacy of antibodies as well as the glucan of Applicant's claimed invention. *See* page 26, lines 5-18, of the Specification and Figure 7.

In the Specification as originally filed, Applicant also described several limitations with existing beta-glucan strategies, such as intravenous administration of lentinan with

antibodies, which have not been addressed or overcome at the time of the filing of this Application, namely:

> (1) The existing beta-glucan preparations are generally expensive and inconvenient to administer, e.g., Lentinan and Schizophyllan are given intravenously daily over long periods of time.
>
> (2) The existing beta-glucan preparations contain proteins and non-β-glucan carbohydrates, which confound mechanistic studies and complicate the manufacturing and control process.
>
> (3) Because of protein contaminants, the existing beta-glucan preparations are potentially allergenic.
>
> (4) The spontaneous cross-linking of CR3 by β-glucan of high MW can cause neutrophil degranulation and cytokine release from macrophages, resulting in undesirable clinical toxicities.
>
> *See* page 69, lines 15-35, of the Specification.
>
> (5) Lentinan is not approved in the US because of its lack of activity and its unacceptable toxicity. Combination of intravenous lentinan and antibodies have toxicity issues that have to be resolved.

The Examiner further states:

> One skilled in the art would be motivated to combine these two teachings to obtain a less evasive, more

> convenient cancer fighting regiment that included oral administration of tumor fighting agents and thus overcome what was once a significant impediment in the art.

In response, Applicant respectfully maintains that there is no motivation, teaching or suggestion to combine Jamas et al. and Herlyn to produce Applicant's claimed invention because, as explained above, Herlyn teaches a method for treating human tumors using monoclonal antibodies together with **intravenously administered** *lentinan glucan, which when administered orally was shown by the Applicant and other investigators to be ineffective {emphasis}*.

As indicated above, Lentinan is ineffective when administered orally, especially in the absence of T-cells, i.e., immune compromised or immune deficient states. *See* abstract on page 4 and page 6, lines 6-8 of Kidd PM. The use of mushroom glucans and proteoglycans in cancer treatment. Altern Med Rev. Vol. 5, p. 4-27 (2000), **Exhibit K**. *See also* page 466, second sentence under paragraph heading "Immunological Activities of Lentinan" of Suzuki et al. Antitumor and immunological activity of lentinan in comparison with LPS. Vol. 16, p. 463-468 (1994), **Exhibit L**. *See also* page 437, second sentence under paragraph heading "Cytotoxic T Lymphocytes and Lentinan" of Chihara et al. Antitumor and Metastasis-Inhibitory Activities of Lentinan as an Immunomodulator: An Overview. Cancer Detect Prev Suppl. Vol. 1, p. 423-443 (1987), **Exhibit M**.

Based on the above literatures, one of ordinary skill in the art would not have expected lentinan to work orally at the time of the filing of this Application. There is no motivation, teaching or suggestion to use or try other glucans derived from other

sources because Herlyn states "the use of lentinan as a macrophage potentiator has been found to be preferred to other possible potentiators because it is relatively safe compound to administer to patients." *See* Herlyn, Col. 2, lines 46-49.

In summary, Applicant respectfully maintains:

1. Changing Parenteral to oral route is not an obvious application of biologics. Indeed, besides being ineffective, changing routes can have the opposite and sometimes damaging effects. Besides pharmacodynamics and bioavailability, mucosal immunity is a critical regulatory component of the immune system and the gut is not just a porthole.

2. The effect of the glucan of Applicant's claimed invention is T-cell independent, and works in both immune competent and immune deficient mammals.

3. The glucan of applicant's claimed invention does not work by cytokine release, which causes clinical toxicity for both PGG and lentinan. For example, barley glucan was used to avoid cytokine release. "Since the chemical composition of (1→3),(1→4)-β-D-glucan derived from barley and oats were similar, comparable levels of synergy with mAb were found, and high m.w. β-glucan was again more effective."

4. The glucan of Applicant's claimed mediates its effect through neutrophils and natural killer cells, but not monocytes or macrophages which also release monokines.

5. Lentinan is too large and too toxic, and is ineffective orally.

Accordingly, Jamas et al. and Herlyn, alone or in combination, does not provide motivation, suggestion or teaching to one of ordinary skill in the art to make or use Applicant's claimed invention.

In addition, the amended claim 67 and new claims 89 and 107 do not contain the above-mentioned issues, thereby rendering this ground of rejection moot. Therefore, Applicant respectfully requests the reconsideration and withdrawal of this ground of rejection.

4. <u>Rejection Under 35 U.S.C. Section 112, Second Paragraph</u>

The Examiner rejected claims 67-87 under 35 U.S.C. section 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states:

> The current claim language is drawn to an activity or desired property of a composition. This language does not particular or distinctly provide sufficient clarity regarding the structure/formulaic/nomenclatorial identity of the chemical core applicants intend to represent as a component of the composition articulated in the claim. In the absence of specific description of what the amount to be administered orally is intended to accomplish, any amount of a glucan administered orally to accomplish any therapeutic result will suffice to meet this limitation of the claim.

In response, but without conceding the correctness of the Examiner's position and to expedite the prosecution of this Application, Applicant has amended claim 67. Claim 67 is directed to a composition comprising foreign antibodies for treating certain cancers and other life-threatening conditions, and the therapeutic effect of the foreign antibodies is synergistically enhanced by orally-administered glucan. New claims 89 and 107 recite "the synergistic therapeutic effect is the eradication or suppression of cancer or tumor cells." One skilled in the art being aware that there is an optimal dosage which will produce synergistic therapeutic effect between foreign antibodies and orally-administered glucan will be able to establish an effective amount or optimal dosage of antibodies and/or orally-administered glucan to accomplish the desired therapeutic result, which includes but is not limited to the treatment of cancer(s). *See* "Phase I study of oral β-glucan and intravenous anti-GD2 monoclonal antibody 3F8 among patients with metastatic neuroblastoma", pages 81-82 of the specification, and page 26, lines 5-18 of the specification.

Accordingly, the new claims do not contain the above mentioned issues, thereby rendering this ground of rejection moot. Therefore, Applicant respectfully requests the reconsideration and withdrawal of this ground of rejection.

CONCLUSION

Applicant respectfully maintains that the rejections raised by the Examiner in the December 17, 2004 Non-final Office Action have been fully addressed. Therefore, this Application is in full compliance with all requirements. Accordingly, Applicant respectfully urges the Examiner to reconsider and withdraw all rejections in the Non-final Office action and place this Application in conditions for allowance.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee other than the EIGHT HUNDRED DOLLARS ($800.00) for the fee for the additional claims and SIXTY DOLLARS ($60.00) for the fee for one-month extension of time is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

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